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New Chiral Ligands for Catalytic Asymmetric Transfer Hydrogenation of Ketones

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Summary: New chiral ligands **3** and **5** have been synthesized. Their Ru(II) complexes are effective catalysts for transfer hydrogenation of both aryl alkyl and dialkyl ketones (with ee's up to 79.5%).
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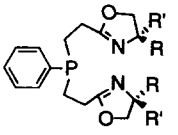
In our previous studies,[1] Ru(II) complexes of NPN-type chiral tridentate ligands (**1**) have shown promising results in catalyzing the asymmetric transfer hydrogenation of ketones.[2] Excellent catalysts based on transition metal complexes with other ligand systems incorporating chelating nitrogen groups have also been reported recently.[3] Regarding the mechanism of this reaction, Noyori has postulated that an NH moiety in some ligands (e.g. **2**) plays a pivotal role in controlling reaction selectivity and activity. By hydrogen bonding with the oxygen atom in ketone substrates, the NH function can help stabilize a cyclic transition state during the step where stereochemistry is established.[3a] Prompted by these reports, we have designed ligands **3** and **4**. Synthesis of **3** was successfully carried out, but attempt to synthesize **4** yielded unexpected products **5**. Both **3** and **5** can form effective catalysts for transfer hydrogenation of ketones, herein some preliminary results are reported.



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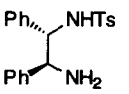

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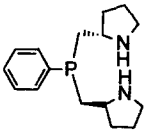

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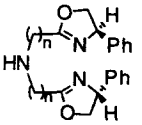

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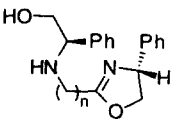

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The preparation of **3** (**Scheme I**) started with readily available Boc-protected L-prolinol, which was almost quantitatively converted to its mesylate **6**. A suspension of $PhPNa_2$ in THF was then slowly added to the mesylate solution in THF. After removal of the Boc group, the crude product was directly converted to **7** by applying BH_3 protection of the phosphorus atom (and possibly one or both NH's as well), followed by column chromatography purification; then pure **3**[4] was quantitatively liberated according to a literature procedure.[5] The

Scheme I

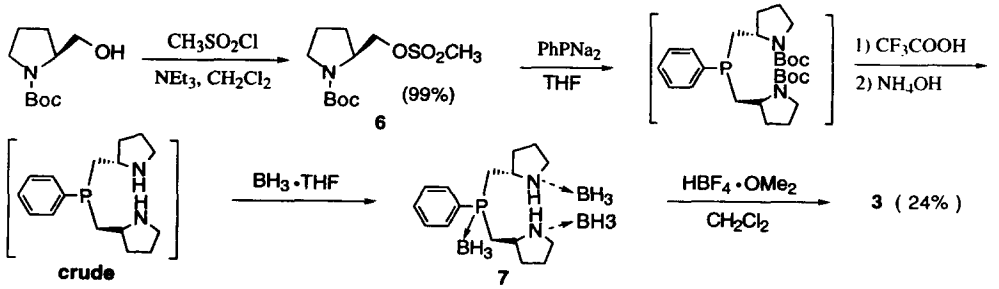
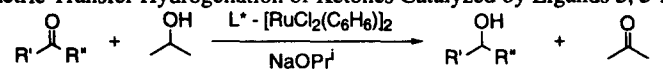
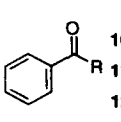


Table 1. Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Ligands **3**, **5**-Ru(II) Complex[a]

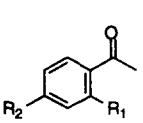


Entry	Ketone	Ligand	T °C	t h	Conversion[b] %	ee[b] %
1	**10**	**3**	23	24	96.0	19.8 (R)
2	**10**	**5a**	23	21	7.0	12.2 (R)
3	**10**	**5b**	23	14	97.3	12.8 (R)
4	**10**	**5b**	0	20	74.1	17.3 (R)
5	**11**	**3**	23	42	93.8	22.6 (R)
6	**11**	**5b**	23	22	98.0	8.2 (S)
7	**12**	**3**	23	42	81.7	30.3 (R)
8	**12**	**5b**	23	22	96.0	20.8 (S)
9	**13**	**3**	23	72	97.7	22.9 (R)
10	**13**	**5b**	23	23	>99	74.8 (S)
11	**13**	**5b**	0	72	96.1	79.5 (S)
12	**14**	**5b**	23	19	98.9	63.1 (S)
13	**15**	**5b**	23	26	>99	55.4 (S)
14	**16**	**5b**	23	20	77.0	9.6 (R)
15	**17**	**5b**	23	20	98.7	0.4 (R)
16	**18**	**5b**	23	23	70.0	38.1 (R)
17	**19**	**5b**	23	25	>99	32.3 (R)
18	**20**	**5b**	23	24	96.6	15.6 (R)
19	**21**	**3**	23	231	91.6	48.5 (S)
20[c]	**21**	**3**	23	160	74.7	61.0 (S)
21	**21**	**5b**	23	24	92.1	46.0 (S)

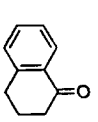
a. Ketone : $NaOPr^i$: Ligand : Ru(II) = 100 : 15 : 1 : 1 molar ratio, [ketone] = 0.1 M. General experimental procedure: To an oven-dried 25 ml Schlenk tube was added $[RuCl_2(C_6H_6)]_2$ (2.5 mg, 0.005 mmol), the ligand solution (0.1 M in toluene, 0.1 mL, 0.01 mmol), 2-propanol (8.5 mL) and $Na[OCH(CH_3)_2]$ solution (0.1 M in 2-propanol, 1.5 mL, 0.15 mmol). The mixture was stirred at rt for 1.5h, followed by addition of the ketone substrate (1 mmol). *b*. Absolute configurations were determined by comparing optical rotations with literature values, %ee and %yield were determined by GC analysis with Supelco β-DEX 120 and γ-DEX 225 capillary chiral columns. *c* In the presence of 0.1 M of $C_6H_5CH(OH)CH_3$ with 12% ee (R).



10 R = CH_3
11 R = CH_2CH_3
12 R = $CH(CH_3)_2$
13 R = $C(CH_3)_3$



14 R_1 = CH_3, R_2 = H
15 R_1 = Br, R_2 = H
16 R_1 = H, R_2 = MeO
17 R_1 = H, R_2 = Br



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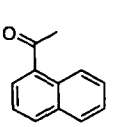

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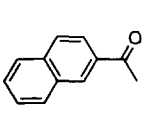

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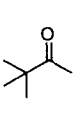
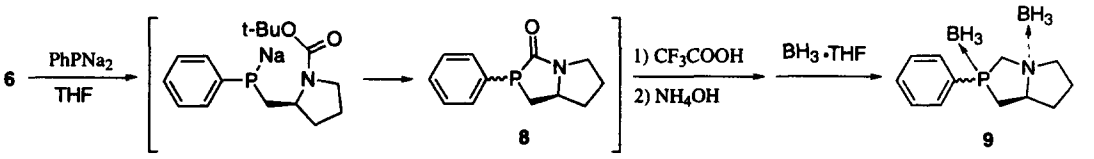


21

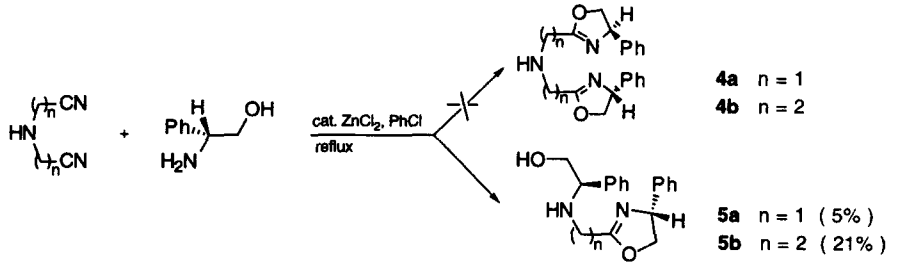
low overall yield for ligand **3** synthesis (24%) is partly due to the fact that two side products are formed during the $PhPNa_2$ addition step (**Scheme II**). The characterization of **8** was performed by NMR analysis, and that of **9** by both NMR and MS. In fact, both diastereoisomers of **9** were easily isolated by column chromatography, and their combined yield was about 50% when the molar ratio of $NaH/PhPH_2$ was 4. We found that a minimum $NaH/PhPH_2$ ratio of 10 was necessary to significantly lower the percentage of these side products.

Scheme II



The attempt to synthesize **4** (**Scheme III**) followed the same strategy as previously reported for **1**.[1] Commercially available iminodiacetonitrile or 3',3-iminodipropionitrile was mixed with 3 equiv. of (R)-2-phenylglycinol in a one-pot reaction catalyzed by 5 mol% $ZnCl_2$, yielding **5a**[6] (5%) and **5b**[7] (21%) (instead of **4a,b**), respectively after chromatographic purification. Since secondary amine functions in the starting dinitriles can form good leaving groups when coordinated to Lewis acids, subsequent nucleophilic attack by the NH_2 group of an amino alcohol becomes possible.

Scheme III



Results for the asymmetric transfer hydrogenation of ketones with these ligands are shown in **Table 1**. First, acetophenone was used as the model substrate for screening ligands and optimizing reaction conditions. As shown by entries 1-4, Ru(II) catalysts formed *in situ* with ligands **3** and **5b** are highly active, while the transfer hydrogenation promoted by Ru(II)-**5a** complex is sluggish and proceeds with poor enantioselectivity. For ligand **3**, pinacolone gave the best enantioselectivity (entries 19, 20). This improvement may be related to the big steric difference between the two sides of the ketone. In addition, entry 20 also shows an interesting "additive effect" in this reaction: in the presence of 0.1 M of very low ee 1-phenylethanol, the enantiomeric excess of pinacolone reduction product was increased by 12%. This increase could be attributed to the lower redox potential of acetophenone than that of pinacolone. Therefore the Ru(II)-**3** complex catalyzes dehydrogenation of 1-phenylethanol faster than that of 3,3-dimethyl-2-butanol.[3a,8] As a result, erosion of the enantiomeric excess due to the reverse process of the transfer hydrogenation of pinacolone is inhibited. Entries 12 to 15 show the catalytic behavior of ligand **5b**: *ortho* -substituted acetophenones can dramatically increase the ee (compare entry 3 to 12 and 13), but *para* -substituted acetophenones have a detrimental effect (entries 14, 15). To our surprise, highly sterically hindered phenyl *t*-butyl ketone was smoothly reduced by the Ru(II)-**5b** complex to its alcohol product

with good enantiomeric excess (entry 10). This remarkable activity even holds at 0°C, with a moderate gain in enantioselectivity as well (entry 11).

We believe that for ligands **3** and **5b**, the NH function of the coordinated ligand may behave as suggested in Noyori's system (**2**),[3a] in which hydrogen bonding exists between ketone substrates and ligands. The high activity for ligands **3** and **5b** shows great potential for further exploring similar systems and achieving good stereoselectivity for a wider scope of ketone substrates. Preparation of our original target ligand system **4** is currently underway.

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4. *Bis[2-(S)-pyrrolidinomethyl]phenylphosphine* (**3**) ^{1}H-NMR ($CDCl_3$): δ = 7.4-7.7 (m, 5H), 4.6 (br, 2H), 3.5 (br, 1H), 2.9-3.4 (m, 5H), 2.7 (dt, J = 13.0, 3.9 Hz, 1H), 2.4 (dd, J = 13.6, 3.7 Hz, 1H), 2.0-2.2 (m, 2H), 1.8-2.0 (m, 8H). ^{13}C-NMR ($CDCl_3$): 134.4 (d, J = 13.5 Hz), 133.3 (d, J = 21.6 Hz), 130.6, 129.0 (d, J = 8.2 Hz), 60.2 (d, J = 28.1 Hz), 58.6 (d, J = 14.0 Hz), 47.7, 47.3, 34.0 (d, J = 12.6 Hz), 32.2 (d, J = 12.0 Hz), 31.8, 31.3 (d, J = 7.9 Hz), 23.8, 23.4. ^{31}P-NMR ($CDCl_3$): δ = -34.1.
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6. *Bis[4-(R)-phenyl-oxazolin-2-yl-methyl]amine* (**5a**) ^{1}H-NMR ($CDCl_3$): δ = 7.2-7.4 (m, 10H), 5.2 (t, J = 8.9 Hz, 1H), 4.5-4.6 (m, 1H), 4.0-4.1 (m, 1H), 3.9 (dd, J = 8.7, 4.0 Hz, 1H), 3.3-3.7 (m, 5H), 3.0 (br, 2H). ^{13}C-NMR ($CDCl_3$): δ = 168.0, 141.8, 140.3, 128.7, 128.5, 127.6, 127.3, 126.5, 74.9, 69.0, 66.7, 64.5, 44.1. IR ($CDCl_3$): 3321 (br), 1668 cm^{-1}. MS (CI) m/e: 297 (M^+ + 1).
7. *Bis[4-(R)-phenyl-oxazolin-2-yl-ethyl]amine* (**5b**) ^{1}H-NMR ($CDCl_3$): δ = 7.2-7.3 (m, 10H), 5.1 (t, J = 9.0 Hz, 1H), 4.4-4.5 (m, 1H), 4.0 (t, J = 8.2 Hz, 1H), 3.8 (dd, J = 8.6, 3.9 Hz, 1H), 3.6 (dd, J = 10.8, 4.1 Hz, 1H), 3.4-3.5 (m, 1H), 2.7-2.9 (m, 2H), 2.4-2.6 (m, 2H), 2.4 (br, 2H, disappeared after D_2O was added). ^{13}C-NMR ($CDCl_3$): δ = 168.0, 142.3, 141.0, 128.7, 128.4, 127.5, 127.3, 126.6, 74.5, 69.3, 66.8, 64.8, 43.6, 28.6. IR ($CDCl_3$): 3387 (br), 1677 cm^{-1}. MS (CI) m/e: 311 (M^+ + 1).
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